# **EXHIBIT E**

August 7, 2006 <u>Time</u> magazine <u>article entitled, "Stem Cells"</u>



WHEN THERE'S NOTHing else to prescribe, hope works like a drug. A quadriplegic patient tells herself it's not a matter of if they find a

cure but when. Who's to say whether salvation is still 10 or 15 years away? After all, researchers have been injecting stem cells into paralyzed rats and watching their spinal cords mend. "Stem cells have already cured paralysis in animals," declared Christopher Reeve in a commercial he filmed a week before he died.

But what is the correct dose of hope when the diseases are dreadful and the prospects of cure distant? Last month, when President George W. Bush vetoed the bill that would have expanded funding for human embryonic-stem-cell (ESC) re-

The debate is so politically loaded that it's tough to tell who's being straight about the real areas of progress and how breakthroughs can be achieved. TIME sorts it out **BY NANCY GIBBS** 

search, doctors got calls from patients with Parkinson's disease saying they weren't sure they could hang on for another year or two. The doctors could only reply that in the best-case scenario, cures are at least a decade away, that hope is no substitute for evidence, that stem-cell science is still in its infancy.

It is the nature of science to mix hope with hedging. It is the nature of politics to overpromise and mop up later. But the politics of stem-cell science is different. Opponents of ESC research—starting with Bush-argue that you can't destroy life in order to save it; supporters argue that an eight-cell embryo doesn't count as a human life in the first place-not when compared with the life it could help save. Opponents say the promise of embryo research has been oversold, and they point



to the cures that have been derived from to the adult stem cells from bone marrow and umbilical cords; supporters retort that adult outcal sare still of limited use, and to fully realize their potential we would need to ly real more about how they operate—which know learn only from studying leftover we can clinic embryos that would otherwise be thrown away.

Back and forth it goes, the politics driving the science, the science pushing back. ing une cell research has joined global warmstem-ing and evolution science as fields in which ing and facts are put to a vote, a public spectne which data wrestle dogma. Scientacle in which data wrestle dogma. tacte who are having surprising success with adult stem cells find their progress being used by activists to progrethat embryo research is not argue argue also unneces-just immoral but also unneces-Just But to those in the field, sary. But sary answer is to press the on all fronts. There are aneau aneau aneau aneau camps for adult stem cells and embryonic stem cells," says Douglas Melton, a co-director ம்பத்தி of the Harvard Stem Gell Inor the se camps only stitute. exist in the political arena. exist is no disagreement among scientists over the need to aggressciences both in order to solve im-

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# Naking Sense of SIEF GELS

## WHATHEYARE

Stem cells are nature's master cells, capable of generating every one of the many different cells that make up the body. They have the ability to selfrenew, which means that they are theoretically immortal and can continue to divide forever if provided with enough nutrients. Because they are so plastic, they hold enormous promise as the basis for new treatments and even cures for disorders ranging from Parkinson's and heart disease to diabetes and even spinal-cord injury

The embryo divides into more and more cells and forms a hollow ball of cells called a blastocyst

Embryonic stem cells begin to form along the inside of the blastocyst, creating the inner cell

from embryos that would other-

wise be wasted is one thing, but scientists admit that moving forward would require a much larger supply of fresh, healthy embryos than fertility clinics could ever provide. And once you start asking people about creating embryos för the purpose of experimenting on them, the support starts to slow down.

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1 EMBRYO

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So where do things stand, five years after Bush provided the first federal funding but radically limited how it could be used?

## HOW RED TAPE SLOWED THE SCIENCE

IN A PRIME-TIME SPEECH FROM HIS TEXAS ranch in August 2001, Bush announced that federal money could go to researchers working on ESC lines that scientists had already developed but no new lines could be

created using federal funds. "There is at least one bright line," he declared. The speech was a political and scientific landmark. It gave Democrats that rare gift. a wedge issue;that split Republicans and united Democrats, who declared themselves the party of progress. Five years later, with midterms looming, they hope to leverage the issue as evidence that they represent the reality-based community, running against the theocrats. States from Connecticut to California have tried to step in with enough funding to keep the labs going and slow the exodus of U.S. talent to countries like Singapore, Britain and Taiwan. Meanwhile, private biotech firms and research universities with other sources of funding are free to

EMBRYO

The most versatile stem cells come from embryos, meaning they are also the most controversial

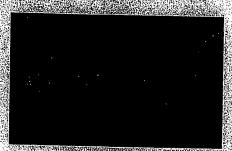
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## WHERE THEY COME FROM

## LEFTOVER OR DEAD END IVE EMBRYOS

Why they are useful More than 400,000. embryos created during in vitro fertilization lie frozen in clinic tanks in the U.S. Many of them will be discarded, so the embryonic stem cells that exist inside them could be salvaged.

prawbacks The freezing process may make it harder to extract stem cells. Some of the embryos were the weakest ones created by infertile couples and may not yield high-quality stem cells.



## NUCLEAR-TRANSFER EMBRYOS

Why they are useful. These embryos are created using the technique that created Dolly, the cloned sheep. Stem cells can be custom-made by inserting a patient's skin cell into a hollowed human egg. Any resulting therapies would not run the risk of immune rejection

Drawbacks The process has not yet been successfully completed with human cells, and it requires an enormous amount of fresh human eggs, which are difficult to obtain

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### **◆ADULT STEM CELLS**

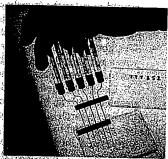
Why they are useful They exist in many major tissues, including the blood skin and brain. They can be coaxed to product more cells of a specific lineage and do not have to be extracted from embryos.

Drawbacks They can generate only a limited number of cell types, and they are difficult to grow in culture

## UMBILICAL CORD CELLS >

Why they are useful Although they are primarily made up of blood stem cells, they also contain stem cells that can turn into bone, cartilage, heart muscle and brain and liver tissue. Like adult stem cells, they are sharvested without the need for embryos

Drawbacks An umbilical cord is not very long and doesn't hold enough cells to treat an adult



COLIN CUTHBERT



TISSUE PRODUCTION
Groups of stem cells are nurtured under specialized conditions, with different recipes of nutrients and growth factors that direct the cells to

become any of the body's more than 200 various tissues

> Pancreatic islet cells Could provide a cure for diabetes

oreate and destroy who have as many embryos as they like; because they operate outside the regulations that follow public funds.

For scientists who choose to work with the approved "presidential lines the funding comes wrapped in frustration. Today there are only 21 viable lines, which limits genetic diversity. They are old, so they don't grow very well. and were cultured using methods that are outdated What's more, the chromosomes undergo subtle changes over time, compromising the cells' ability to remain "normal" Back in the late '90s, when the lines were oreated, "we didn't know much about growing stem cells," says Kevin Eggan, principal faculty member at the Harvard Stem Cell Institute: "They can't do what the newer cell lines can do." Gurt Civin, a cancer researcher at Johns Hopkins, has spent the

past's everal years trying to differ a entiate the presidential lines into blood cells that could be used to treat leukemias and other blood based can cers. But the age and quality of the cells have been a constant hindrance. "We want

to study normal cells," he says, "We're working with Version I.O. I'd like Version 3.3."

The presidential lines, scientists say, are wasting money as well as time. Larry Golds

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Graph

stein's lab at the University of California at

San Diego is a life-size game of connect the dots. Each machine, cell dish, chemical and pretty much every major tool bears a colored dot, signaling to lab workers whether they can use the item for experiments that the government won't pay for. Goldstein's team is working on a cancer experiment that relies on a \$200,000 piece of equipment. They can use either an approved cell line that will yield a less reliable result or a freshly created line that would require the purchase of another machine with private funds. "It's a ball and chain," Goldstein says. "It's goofy. Imagine if your kitchen was a mixture like that, where you can't use those pots with that soup." Congress tried to address the

problem with its bill to allow funding for research on any leftover embryos donated by infertility patients. But even if Bush hadn't vetoed the bill, it wouldn't have solved the supply problems. One study estimated that at best, a couple hundred cell lines might be derived from leftover IVF embryos, which tend to be weaker than those implanted in patients. The very fact that they

planted in patients. The very fact that they come from infertile couples may mean they are not typical, and the process of freezing and thawing is hard on delicate cells.

## SOLVING A PROBLEM CREATED NEW ONES

IN THE WAKE OF BUSH'S ORIGINAL ORDER, Harvard decided to use private funding to develop about 100 new cell lines from fertility-clinic embryos, which it shares with researchers around the world. Scientists, desperate for variety, snap them up. "Not all embryonic-stem-cell lines are created equal," says Dr. Arnold Kriegstein, who runs the Institute for Regeneration Medicine at the University of California, San Francisco. "Some are more readily driven down a certain lineage, such as heart cells, while others more easily become nerve. We don't understand how it happens, but it does mean we need diversity."

At the same time, Harvard has opened another battleground in the search for cells. After exhaustive ethical review, its researchers announced this summer that they would develop new cell lines through somatic cell nuclear transfer, or therapeutic cloning. In this process, a cell from a patient with diabetes, for instance, is inserted into an unfertilized egg whose nucleus has been removed; then it is prodded into growing in



a petri dish for a few days until its stem cells can be harvested. Unlike fertility-clinic embryos, these cells would match the patient's DNA, so the body would be less likely to reject a transplant derived from them. Even more exciting for researchers, however, is that this technique can yield embryos that serve as the perfect disease in a dish, revealing how a disease unfolds from the very first hours.

The long-term promise is boundless, but the immediate barriers are high. The only people who claim to have succeeded in creating human-stem-cell lines through nuclear transfer were the South Korean researchers who turned out to be frauds. It will take much trial and error to master the process, but where do you get the human eggs needed for each attempt, particularly since researchers find it ethically inappropriate to reimburse donors for anything but expenses? And even if the technique for cloning embryos could be perfected, would Congress allow it to go on?

# THE HUNT FOR NEW SOLUTIONS

TO GET AROUND POLITICAL ROADBLOCKS, scientists are searching for another source of cells that is less ethically troublesome, ideally one that involves no embryo de-

ATHE PROCESS

Stem cells can be found in embryos, some adult cells and even in the umbilical cords of newborns

struction at all. One approach is "altered nuclear transfer," in which a gene, known as CDX2. would be removed before the cell is fused with the egg. That would ensure that the embryo lives only long enough to produce stem cells and then dies. That strategy, promoted by Dr. William Hurlbut. a member of the President's Council on Bioethics, has its critics. Dr. Robert Lanza of biotech firm Advanced Cell Technology considers it unethical to deliberately create a crippled human embryo "not for a scientific or medical reason, but purely to address a religious issue." The most exciting new possibility doesn't go near embryos at all. Dr.



from replacement neurons, while diabetics who can't produce insulin could control their blood sugar with new pancreatic islet cells. But so far, no human escs have been differentiated reliably enough that they could be safely transplanted into people, although animal studies with human cells are under way. Not surprisingly, the groups closest to human trials are in the biotech industry, which operates without government funds. Geron claims it is close to filing for permission to conduct the first human trials relying on Esc-based therapy. It is using stem cells to create oligodendroglial progenitor cells, which produce neurons and provide myelin insulation for the long fingers that extend out from the body of a nerve cell. Lanza's group is also close to filing for FDA permission to begin clinical trials on three cell-based therapies: one for macular degeneration, one for repairing heart muscle and another for regenerating damaged skin. Not to to be outdone, the academic groups are just a few steps behind. Lorenz Studer at Memorial Sloan-Kettering Cancer Center in New York City has been able to differentiate ESCs into just about every cell type affect-

mobility Next, he plans to inject the cells into monkeys. THE RISKS ON THE NEW. FRONTIER

BUT THE CLOSER SCIENTISTS COME TO HUman trials, the more concerned the FDA will be with ensuring patient safety. The government will look at how the cells were grown and whether there would be risk of contamination from animal products used in the process. Regulators want data on how the cells will behave in the human body. Stem cells have shown a dismaying talent for turning into tumors. Will they migrate into unwanted areas? No one knows. You can't find out for sure until you test in humans, but it's hard to test in humans until you can be reasonably sure you won't harm them in the process.

When human trials finally begin, there's no method for precisely determining whether the transplanted stem cells are functioning correctly. "If we transplanted cells to regenerate a pancreas," says Owen Witte, director of UCLA's In-

ed by Parkinson's disease and has transplanted them into rats and improved their EMBRYO Shinya Yamanaka of Kyoto University re-A technician ported tantalizing success in taking an adult with embryonic skin cell, exposing it to four growth factors stem cells, top left in a petri dish and transforming it into an which grow rapidly under the right conditions embryo-like entity that could produce stem cells—potentially sidestepping the entire A D ULT CELLL Bone-marrow cells, top right, can debate over means and ends. Even if scientists discover an ideal generate blood and immune cells source of healthy cell lines, there is still much to learn about how to coax them into CORDBLOOD Umbilical-cord cells, in pouch, above turning into the desired kind of tissue. right, can produce blood, heart, brain. Parkinson's patients suffering from tremors and liver cells in culture

caused by damaged nerves could benefit

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stitute for Stem Cell Biology and Medicine, "we can measure in your blood if you're producing insulin, but we can't see whether the cells have grown or evaluate whether they might grow into a tumor So scientists are seeking to develop marking systems that let them trace a transplants performance.

## and the second section of the second THE PROMISE AND PITFALLS OF ADULT CELLS

EVEN AS SCIENTISTS PRESS AHEAD WITH embryo research, exciting news has come from the least controversial sources: the stem cells in umbilical-cord blood and placentas, and even in fully formed adult organs. While not as flexible as embryonic cells, cord and placental cells have proved more valuable than scientists initially hoped. Although about 90% of cordblood stem cells are precursors for blood and immune cells, the remaining 10% give rise to liver, heart-muscle and brain cells and more. Over the past five years. cord-blood transplants have become an increasingly popular alternative to bonemarrow transplants for blood disorders, particularly when a bone-marrow match can't be found. The secretary and entire

If you want to lean out over the edges of science and marvel at what is now possible, visit Dr. Joanne Kurtzberg's program at Duke University Medical Center. Children with blood diseases that were almost certainly fatal a decade ago have got cord-blood transplants that essentially cure them. Now she and her team are taking a more targeted approach by attempting to differentiate cord-blood cells to address heart, brain and liver defects. "I think cord-blood cells have a lot of promise for tissue repair and regeneration," says Kurtzberg. "But I think it will take 10 to 20 years."

Less plastic than cord-blood cells are adult stem cells, which until recently researchers thought couldn't do much more than regenerate cell types that reflected the stem cells' origin-blood and immune cells from bone marrow, for example. Even so,

It takes only a week for

some scientists believe adult stem cells may prove to be a powerful source of therapies "In some cases, you may not want to go all the way back to embryonic stem cells," says Kurtzberg, "You may want something more specific or less likely to stray. You wouldn't want to put a cell in the brain and find out later that it turned into bone?

Researchers in Thailand have taken stem cells from the blood of cardiac patients, grown the cells in a lab and reinjected them into patients' hearts, where they set about repairing damage. Two UCLA researchers last week published a study demonstrating that they could transform adult stem cells from fat tissue into smooth-muscle cells, which assist in the function of numerous organs. Welcome as the advances are the subject of adult stem cells is highly political and invites a conflation of real hopes and false ones: "There are papers that have claimed; broad uses for certain adult stem cells and some people say that is sufficient. cause to not work on embryonic steme cells," Witte says: "Many of those claims were overblown."

Even the true believers among scientists, however, dispute eager politicians who have called for a Manhattan Project approach to research "I hate to say it, but biology is more complicated than splitting the atom," Witte says. "The physicists on the Manhattan Project knew what they needed to accomplish and how to measure it. In biology, we're codeveloping our measurement tools and our outcome tools at the same time." Indeed, a massive centralized effort controlled by the Federal Government could do more harm than good. The key is to have the broadest cross section of scientists possible working across the field. When it comes to such an impossibly complicated matter as stem cells, the best role for legislators and Presidents may be neither to steer the science nor to stall it but to stand aside and let it breathe.

-Reported by Alice Park/New York

and Dan Cray/Los Angeles embryonic stem cells to blanket the inside of a rapidly dividing blastocyst



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S C I E N C E



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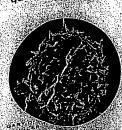
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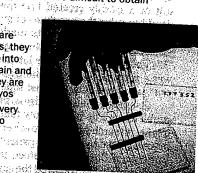
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The presidential lines, scientists say, are wasting money as well as time. Larry Goldstein's lab at the University of California at

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San Diego is a life-size game of connect the dots. Each machine, cell dish, chemical and pretty much every major tool bears a colored dot, every ling to lab workers whether they can use the item for experiments that the government won't pay for. Goldstein's team is working Par a cancer experiment that relies on a \$200,000 piece of equipment. They can use either an approved cell line that will yield a less reliable result or a freshly created line that would require the purchase of another machine with private funds. otris a ball and chain," Goldstein says. "It's goofy. Imagine if your kitchen was a mixture like that, where you was tuse those pots with that soup." Congress tried to address the

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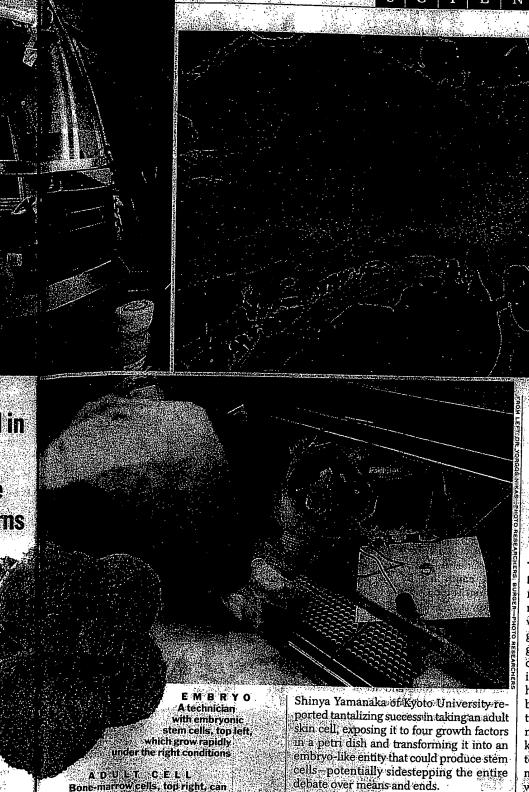
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ATHE PROCESS

Stem cells can be found in embryos, some adult cells and even in the umbilical cords of newborns

struction at all. One approach is "altered nuclear transfer," in which a gene, known as CDX2, would be removed before the cell is fused with the egg. That would ensure that the embryo lives only long enough to produce stem cells and then dies. That strategy, promoted by Dr. William Hurlbut, a member of the President's Council on Bioethics, has its critics. Dr. Robert Lanza of biotech firm Advanced Cell Technology considers it unethical to deliberately create a crippled human embryo "not for a scientific or medical reason, but purely to address a religious issue." The most exciting new possibility doesn't go near embryos at all. Dr.



generate blood and immune cells

Umbilical-cord cells, in pouch, above

right; can produce blood, heart, brain

CORD BLOOD

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sulin could control their blood sugar with new pancreatic islet cells. But so far, no human ESCs have been differentiated reliably enough that they could be safely transplanted into people, although animal studies with human cells are under way. Not surprisingly, the groups closest to human trials are in the biotech industry, which operates without government funds. Geron claims it is close to filing for permission to conduct the first human trials relying on ESC-based therapy. It is using stem cells to create oligodendroglial progenitor cells, which produce neurons and provide myelin insulation for the long fingers that extend out from the body of a nerve cell. Lanza's group is also close to filing for FDA permission to begin clinical trials on three cell-based therapies: one for macular degeneration, one for

from replacement neurons, while diabetics who can't produce in-

repairing heart muscle and another for regenerating damaged skin. Not to to be outdone, the academic groups are just a few steps behind. Lorenz Studer at Memorial Sloan-Kettering Cancer Center in New York City has been able to differentiate ESCs into just about every cell type affected by Parkinson's disease and has transplanted them into rats and improved their mobility Next, he plans to inject the cells

into monkeys.

Even if scientists discover an ideal

source of healthy cell lines, there is still

much to learn about how to coax them into

turning into the desired kind of tissue.

Parkinson's patients suffering from tremors

caused by damaged nerves could benefit

## THE RISKS ON THE NEW FRONTIER

BUT THE CLOSER SCIENTISTS COME TO HUman trials, the more concerned the FDA will be with ensuring patient safety. The government will look at how the cells were grown and whether there would be risk of contamination from animal products used in the process. Regulators want data on how the cells will behave in the human body. Stem cells have shown a dismaying talent for turning into tumors. Will they migrate into unwanted areas? No one knows. You can't find out for sure until you test in humans, but it's hard to test in humans until you can be reasonably sure you won't harm them in the process.

When human trials finally begin, there's no method for precisely determining whether the transplanted stem cells are functioning correctly. "If we transplanted cells to regenerate a pancreas," says Owen Witte, director of ucla's In-

stitute for Stem Cell Biology and Medicine, "we can measure in your blood if you're producing insulin, but we can't see whether the cells have grown or evaluate whether they might grow into a tumor." So scientists are seeking to develop marking systems that let them trace a transplant's performance.

## THE PROMISE AND A MARCH PITFALLS OF ADULT CELLS

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EVEN AS SCIENTISTS PRESS AHEAD WITH embryo research, exciting news has come from the least controversial sources: the stem cells in umbilical-cord blood and placentas, and even in fully formed adult organs. While not as flexible as embryonic cells, cord and placental cells have proved more valuable than scientists intially hoped. Although about 90% of cord blood stem cells are precursors for blood and immune cells, the remaining 10% give rise to liver, heart-muscle and brain cells and more. Over the past five years. cord-blood transplants have become an increasingly popular alternative to bonemarrow transplants for blood disorders, particularly when a bone-marrow match can't be found. one bur with our de

If you want to lean out over the edges of science and marvel at what is now possible, visit Dr. Joanne Kurtzberg's program at Duke University Medical Center. Children with blood diseases that were almost certainly fatal a decade ago have got cord-blood transplants that essentially cure them. Now she and her team are taking a more targeted approach by attempting to differentiate cord-blood cells to address heart, brain and liver defects: "I think cord blood cells have a lot of promise for tissue repair and regeneration," says Kurtzberg. "But I think it will take 10 to 20 years."

Less plastic than cord-blood cells are adult stem cells, which until recently researchers thought couldn't do much more than regenerate cell types that reflected the stem cells origin-blood and immune cells from bone marrow, for example. Even so. and the

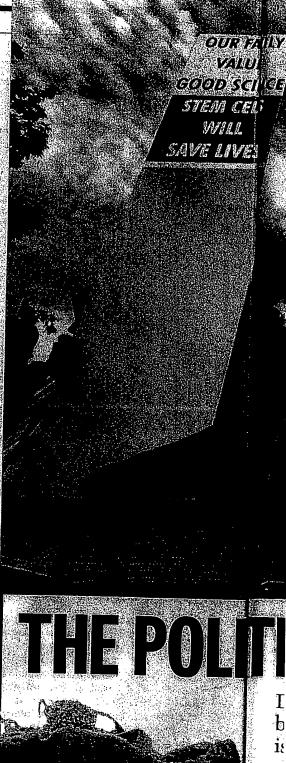
some scientists believe adult stem cells may prove to be a powerful source of therapies. "In some cases, you may not want to go all the way back to embryonic stem cells," says Kurtzberg. "You may want something more specific or less likely to stray. You wouldn't want to put a cell in the brain and find out later that it turned into bone."

Researchers in Thailand have taken stem cells from the blood of cardiac patients, grown the cells in a lab and reinjected them into patients' hearts, where they set about repairing damage. Two UCLA researchers last week published a study demonstrating that they could transform adult stem cells from fat tissue into smooth-muscle cells, which assist∋in the function of numerous organs. Welcome as the advances are the subject of adult stemicells is highly political and invites a conflation of real hopes and false ones. "There are papers that have claimed broad uses for certain adult stem cells, and some people say that is sufficient cause to not work on embryonic stem cells," Witte says. "Many of those claims were overblown.

Even the true believers among scientists, however, dispute eager politicians who have called for a Manhattan Project approach to research. "I hate to say it, but biology is more complicated than splitting the atom," Witte says "The physicists on the Manhattan Project knew what they needed to accomplish and howeto measure it. In biology, we're codeveloping our measurement tools and our outcome tools at the same time." Indeed, a massive centralized effort controlled by the Federal Government could do more harm than good. The key is to have the broadest cross section of scientists possible working across the field. When it comes to such an impossibly complicated matter as stem cells, the best role for legislators and Presidents may be neither to steer the science nor to stall it but to stand aside and let it breathe.

-Reported by Alice Park/New York and Dan Cray/Los Angeles

THE CELLS It takes only a week for embryonic stem cells to blanket the inside of a rapidly dividing blastocyst



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